

# Mixed Adeno and Neuroendocrine Carcinoma of The Ovary: Case Report

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## ABSTRACT

*Reporting two cases of mixed adenocarcinoma and neuroendocrine carcinoma of the ovary. A case report two cases of an ovarian cyst suspect malignancy after complete surgical staging in woman aged 39 year old and 72 year old. By this case report, we want to know prognosis of the malignancy. Mixed adenocarcinoma and neuroendocrine carcinoma of the ovary of the first case arised from mature cystic teratoma, and second case as metastatic process from gastrointestinal tract. Mixed adenocarcinoma and neuroendocrine carcinoma is rare hystologic type of ovarian cancer. Need further exploration to know the survival of this hystologic type.*

**Keywords:** *mixed adenocarcinoma and neuroendocrine carcinoma, ovary, surgical staging*

## ABSTRAK

Artikel ini melaporkan dua kasus, yaitu *mixed adenocarcinoma* dan *neuroendocrine carcinoma ovarium*, dua kasus kista ovarium curiga ganas pada pasien berusia 39 tahun dan 72 tahun. Terhadap kedua pasien dilakukan komplit *surgical staging*. Melalui laporan kasus ini, diharapkan bisa diketahui prognosis kasus. *Mixed adenocarcinoma* dan *neuroendocrine carcinoma ovarium* pada kasus pertama timbul dari teratoma matur kistik, sedangkan kasus kedua merupakan penyebaran dari traktus digestivus. *Mixed adenocarcinoma* dan *neuroendocrine carcinoma* merupakan tipe histologi kanker ovarium yang jarang. Ia membutuhkan eksplorasi lebih lanjut untuk mengetahui *survival* dari tipe histologi ini.

**Kata Kunci:** *mixed adenocarcinoma dan neuroendocrine carcinoma, ovarium, surgical staging*

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## INTRODUCTION

Approximately 75–80% of epithelial ovarian cancers are serous hystologic type, with the majority being high grade cancers. Less common subtypes are mucinous (10%), endometrioid (10%), clear cell, Brenner and undifferentiated carcinomas. Each tumor type has a hystologic pattern that recapitulates the epithelial features of a section of the lower genital tract. Although epithelial ovarian cancer is often thought of as a single entity, the different hystologic types are variable in their behavior. Commonly, two or more cell types are mixed. Within each hystologic type, tumors are further categorized as benign, borderline (low malignant potential) or malignant. Adenocarcinoma is derived from mucinous tumor, that categorized as malignant tumor.

Neuroendocrine tumors consist of a spectrum of malignancies that arise from the diffuse neuroendocrine cell system. Prognosis is dependent on histologic subtype and site of origin. The family of well differentiated neoplasms (i.e. carcinoid and atypical carcinoid) is morphologically and clinically distinct from high-grade neuroendocrine carcinoma (i.e., small cell and large cell). This latter entity is closely related to pulmonary small-cell carcinoma, is highly aggressive, and is generally managed with a multimodality approach including platinum based chemotherapy. Well and poorly differentiated neuroendocrine tumors are grouped together only because of generic neuroendocrine marker expression (i.e. expression of the markers synaptophysin and chromogranin detected by immunohistochemistry).<sup>1</sup> The biology and clinical outcome of poorly differentiated neuroendocrine carcinomas, however, are vastly different from the well differentiated neuroendocrine tumors. In recent decades, there has been an increased reported incidence of neuroendocrine tumors, which may reflect improvements in standardized classification criteria, and increased diagnostic recognition. Neuroendocrine tumors primary to the gynecologic tract are still considered to be uncommon, with limited prospective data from which to guide decisions.<sup>2</sup> This case report, reported rarely case of mixed adenocarcinoma and neuroendocrine carcinoma. There were limited data of this case. By this case report, we can learn how to manage the patient and also prognosis of this malignancy.

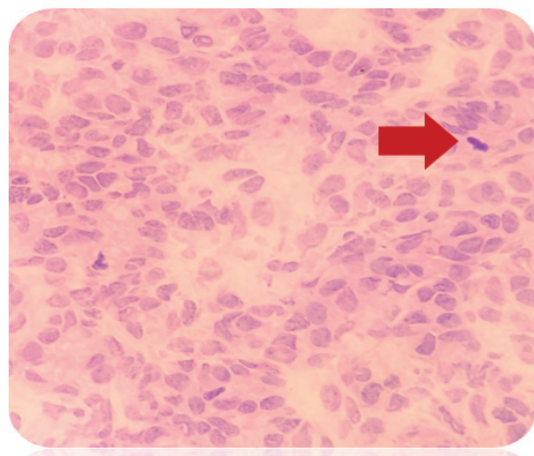
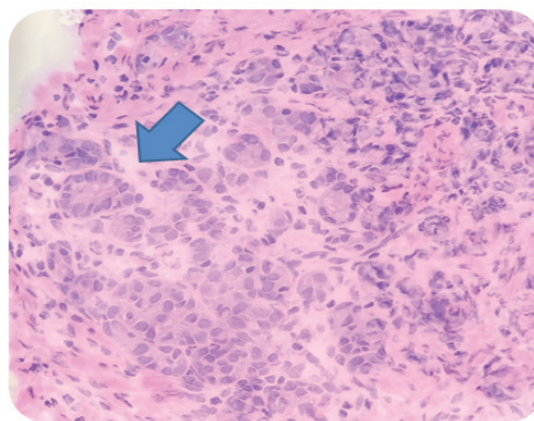
## CASE REPORT

### First Case

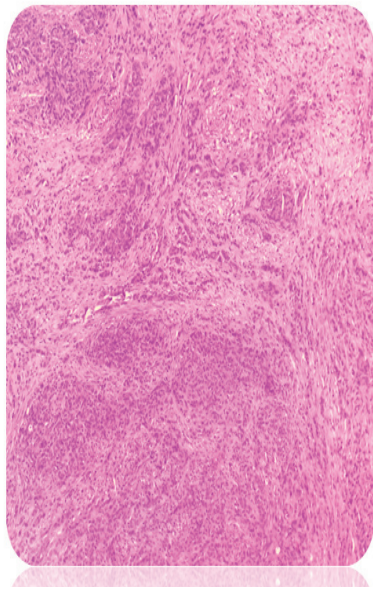
A woman of 39 year old complained about an abdominal enlargement and also abdominal discomfort. Patient without living child and married for 6 years. Gynecological examination of internal genital organ and the mass, was difficult to, because of massive ascites. Ultrasound examination found hypohyperechoic mass with diameter 10.1x4.83 cm, irregular border and seen ascites. Tumor markers examination show increased of Ca-125 (414.2), Ca 19-9 > 500. The patient underwent laparotomy (unilateral salpingo-oophorectomy)-frozen section. During operation, 2000 cc ascites was found and sent for cytologic examination. Cystic mass with solid part was found from right adnexa with diameter 20x15 cm, irregular surface. Done right salpingo-oophorectomy and frozen section. From left adnexa found mixed cystic and solid mass with

diameter 10x10 cm. Frozen section result was mixed germ cell and sex cord stromal tumor, seems mixed type of mature teratoma and granulosa cell tumor. Cytology result was reactive mesothelial hyperplasia. The operation continued with complete surgical staging (total abdominal hysterectomy, left salpingo-oophorectomy, omentectomy, appendectomy, bilateral pelvic lymphadenectomy, paraaortic lymphadenectomy and peritoneal biopsy).

Pathology anatomy result were: mixed adeno and neuro endocrine carcinoma (MANEC) arising in mature cystic teratoma from both ovaries dd/MANEC metastasis from another organ. To ensure tumor type of neuroendocrine carcinoma, immunochemistry examination (Chromogranin, neurospecific-enolase and synaptophysin) was done. Conclusion of immunochemistry was support neoplasm with neuroendocrine feature. But these examination can not used to enactive tumor biologic behavior.



**Figure 1:** Frozen section microscopically: tubular structure covered by cuboid epithelium (blue arrow), cells with increase of N/C ratio, irregular nucleus membrane, hyperchromatic, found mitotic process (red arrow)



**Figure 2:** Tumor mass consist of proliferated neoplastic epithel cells, in clusters and trabecular pattern infiltrative in the desmoplastic stroma.

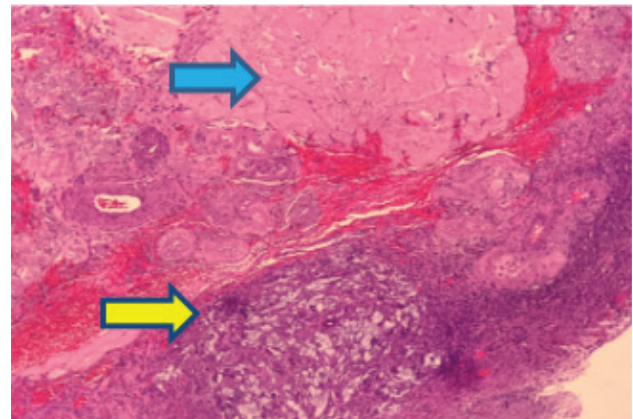
This patient plan to receive adjuvant chemotherapy which give Gemcitabine Carboplatin regimen for sixth series. Carboplatin dose will give based on area under curve-5 and Gemcitabine dose will give 1000 mg/m<sup>2</sup> body surface area. Spacing of each chemotherapy is every 3 weeks. After each series of chemotherapy, will do clinical evaluation and tumor marker evaluation to know chemotherapy response.

## Second Case

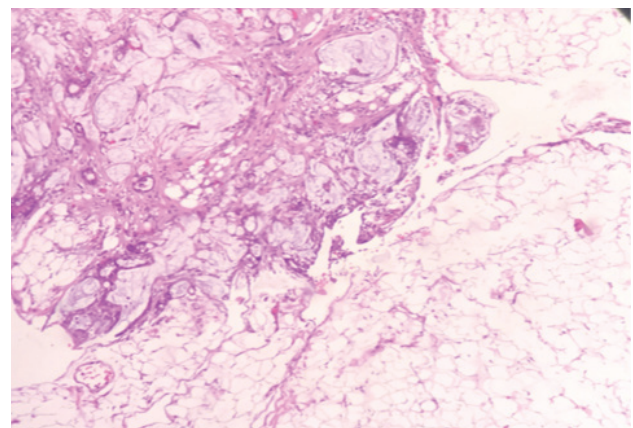
A woman of 72 year old complained about an abdominal enlargement and also abdominal discomfort. Patient without living child and married for 45 years. Gynecological examination found cystic mass with solid part with diameter 30 x 25 cm, clear border and mobile. Ultrasound examination found hypohyperechoic mass with unmeasured diameter, multilocular and seen no ascites. Tumor markers examination show increased of Ca-125 (105.5), Ca 19-9 > 16.17. The patient underwent laparotomy (right salphingooforectomy)-frozen section. During operation found minimal ascites and done cytology examination of ascites. Found cystic mass with solid part from right adnexa with diameter 20x15 cm, irregular surface. Done right salphingoophorectomy and frozen section. From left adnexa found within normal limit. Frozen section result was mucinous carcinoma. Cytology result was atypic mesothelial cell. The operation continued with complete surgical staging (total abdominal hysterectomy, left salphingoophorectomy,

omentectomy, appendisectomy, bilateral pelvic lymphadenectomy, and peritoneal biopsy).

Pathology Anatomy result were: mixed adeno and neuro endocrine carcinoma (MANEC) from left ovary and appendix (mucinous adenocarcinoma with signet ring cell component and goblet cell carcinoma), extent to uterus, suggested arising from appendix. And malignant cell metastatic to right and left paracolic peritoneum and omentum. To confirm primary tumor arising from ovaries or appendix by IHC CK 7 and CK 20 examination. To ensure tumor type of neuroendocrine carcinoma, immunochemistry examination (chromogranin, neurospecific-enolase and synaptopisin) was done. Conclusion of immunochemistry examination were neoplasm originated from gastrointestinal tract, with neuroendocrine differentiation.



**Figure 3:** Tumor mass consist of proliferated of neoplastic epithel cells, infiltrative in the ovarian stroma (yellow arrow). Corpus albicans (blue arrow)



**Figure 4:** Neoplastic invasion in omentum with similar pattern

This patient plan to receive adjuvant chemotherapy which give Paclitaxel Carboplatin regimen for sixth series. Carboplatin dose will give based on area



under curve-5 and Paclitaxel dose will give 175 mg/m<sup>2</sup> body surface area. Spacing of each chemotherapy is every 3 weeks. After each series of chemotherapy, will do clinical evaluation and tumor marker evaluation to know chemotherapy response.

## DISCUSSION

Neuroendocrine tumors are neoplasms with a broad range of morphologic patterns, grade of differentiation and biologic behavior that share common features of neuroendocrine programming. Neuroendocrine tumors contain various amount of molecules involved in regulated release of neuropeptide, neurotransmitters and hormones. Most neuroendocrine tumors are of endodermal derivation and rare entities of rare entities of true neural crest origin. They may occur in every topographic location, with a predilection of lung, intestine and pancreas. Other primary organs include the skin, salivary gland, prostate and various sites in the urinary, genital and biliary tracts.<sup>1,3</sup>

Mature cystic teratoma usually was benign condition, which consist of three layers of germinal cell: ectoderm, mesoderm and endoderm.<sup>4,5,6,7</sup> But, in rare condition, mature cystic ovary can become malignant transformation in one of its component. Malignant transformation of mature cystic teratoma is a rare condition, happen in 2% from all of ovarian malignancy cases. In one of reference, explained that neuroendocrine component (*mucinous carcinoid ovarian tumor*) found in mature cystic teratoma of 1/3 cases.<sup>8</sup> This teratoma component support origin of ovarian tumor. Primary ovarian tumor is very rare and only found in about 0.1% of ovary.<sup>9</sup>

Neuroendocrine cells have been identified in normal epithelium of the female genital tract. Ovarian neuroendocrine tumors may develop from non neuroendocrine cells in which there has been activation of genes that promote neuroendocrine differentiation. In the 2000 WHO classification of endocrine tumors, such neoplasms were defined as mixed exocrine-endocrine tumors when each component represents at least 30% of the lesion. In the most recent WHO classification of neoplasms of the gastrointestinal tract, such neoplasms are called "mixed adenoneuroendocrine carcinomas" (MANECs).<sup>10,11</sup>

The presence of a neuroendocrine component in gastrointestinal adenomas/adenocarcinomas has often been reported. Indeed, the systematic application of immunohistochemical techniques to the study of

gastrointestinal tumors has demonstrated that neuroendocrine cells occur rather frequently in non-endocrine neoplasms. Similarly, the presence of an exocrine component in gastrointestinal neuroendocrine neoplasms, especially in high grade neuroendocrine carcinomas, has also been widely documented. There is a wide spectrum of such combinations of exocrine and neuroendocrine components, ranging from adenomas or carcinomas with interspersed neuroendocrine cells on the one end to classical neuroendocrine tumors with a focal exocrine component on the other end. In addition, both the exocrine and the neuroendocrine components can have different morphological features ranging from adenomas to adenocarcinomas with different degrees of differentiation in exocrine components and from well differentiated to poorly differentiated neuroendocrine tumors in neuroendocrine components. However, although this spectrum of combinations is frequently observed in routine practice, mixed exocrine-neuroendocrine tumors are rarely found. By definition, such neoplasms are those in which each component represents at least 30% of the lesion.<sup>10,11</sup>

Mixed adenoneuroendocrine carcinomas (MANECs) are morphologically recognizable as both gland forming epithelial and neuroendocrine neoplasms and they are defined as carcinomas since both components are histologically malignant. An exocrine component of squamous cell carcinoma, although very rare, can also be observed, especially in esophageal and anal tumors. It is worth noting that adenocarcinomas with scattered neuroendocrine cells, shown by immunohistochemistry, cannot be categorized as MANECs, nor can neuroendocrine neoplasms with a focal non-neuroendocrine component. Although goblet cell carcinoids of the appendix have been traditionally considered as mixed exocrine-neuroendocrine neoplasms, in the 2010 WHO classification of tumors of the digestive system they have been described in both adenocarcinoma and neuroendocrine tumor sections, giving rise to some confusion. Appendiceal tubular carcinoids, although able to produce mucins focally, are classified among neuroendocrine neoplasms in the 2010 WHO classification and for this reason we do not include them in the present paper. However, it is worth noting that these particular appendiceal neoplasms require further investigation to better clarify their histogenesis, molecular profile and, consequently, classification. In some MANECs the neuroendocrine and exocrine components occur in separate areas of the same lesion (composite or collision neoplasms),

while in other MANECs they are intimately and diffusely admixed (combined neoplasms). The clinical significance and the influence on survival of focal neuroendocrine differentiation in gut adenocarcinomas still remain controversial. MANECs may constitute a diagnostic challenge because frequently only one component of the neoplasm is identified. This leads to an incomplete diagnosis and suboptimal treatment.<sup>10,11</sup>

In the first case difficult to certain origin of the primary tumor, because from appendix found neuroendocrine tumor which can metastatic to ovaries. And in the other side, in the ovary found neuroendocrine component in teratoma which metastatic to appendix, contralateral ovary, vaginal cuff, cervix, uterus, omentum, paraaortic lymph node and douglas cavity.

First patient in this case report received adjuvant chemotherapy which give Gemcitabine Carboplatin for sixth series. After sixth series of chemotherapy, there were no clinical sign of new mass and tumor markers in the normal range. Mixed adeno and neuroendocrine carcinoma of the ovary is very rare case. By limited data or case report of MANECs of the ovary, prognosis of this case still observed. Second patient refused to receive adjuvant chemotherapy.

## CONCLUSION

Neuroendocrine tumors of the gynecologic tract comprise a spectrum of entities of variable biologic potential. Although rare, accurate diagnosis of such entities is important for both therapeutic and prognostic purposes.

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